All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼)
85 micrograms/43 micrograms inhalation powder as hard capsules

Reference number: 1535

LIMITED SUBMISSION

This report has been prepared by the All Wales Therapeutics and Toxicology Centre (AWTTC), in collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University.

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre (AWTTC)
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 2071 6900

This report should be cited as:
All Wales Therapeutics and Toxicology Centre. AWMSG Secretariat Assessment Report. Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼)
85 micrograms/43 micrograms inhalation powder as hard capsules.
Reference number: 1535. February 2014.

AWMSG Secretariat Assessment Report
Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼)
85 micrograms/43 micrograms inhalation powder as hard capsules

This assessment report is based on evidence from a limited submission by Novartis Pharmaceuticals Ltd on 25 October 2013[1].

1.0 PRODUCT AND APPRAISAL DETAILS

Licensed indication under consideration	Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease[2].
Dosing	The recommended dose is the inhalation of the content of one capsule once daily using the Ultibro® Breezhaler®▼. Each delivered dose contains 110 micrograms of indacaterol maleate (equivalent to 85 micrograms of indacaterol) and 54 micrograms of glycopyrronium bromide (equivalent to 43 micrograms of glycopyrronium)[2].
Marketing authorisation date	19 September 2013[3]
UK launch date	[Commercial in confidence data removed]
Comparators	The comparator included in the company submission was indacaterol inhalation powder (Onbrez® Breezhaler®) in conjunction with glycopyrronium inhalation powder (Seebri® Breezhaler®▼)[1].
Limited submission details	Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) for the above indication met the following criteria for eligibility for a limited submission: • Significant new formulation with a pro-rata or lower cost per treatment. • Anticipated usage in NHS Wales is considered to be of minimal budgetary impact. • Estimated small difference in cost compared to comparator.

2.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission included a clinical study, BEACON, which was designed to evaluate the non-inferiority of the efficacy and safety of treatment with indacaterol/glycopyrronium as a combination product (Ultibro®) versus treatment with indacaterol (Onbrez®) and glycopyrronium (Seebri®) given separately in patients with chronic obstructive pulmonary disease (COPD; see Glossary)[1,4]. The treatments were administered using Breezhaler® inhalers.

2.1 Clinical evidence

BEACON was a multicentre, double-blind, parallel-group study, which investigated the efficacy and safety of indacaterol and glycopyrronium given as a combination product in patients (≥ 40 years) with moderate to severe COPD[4]. Following a screening/washout period and a run-in period, patients (n = 193) were randomised 1:1 to receive once daily indacaterol/glycopyrronium combination product (110 micrograms of indacaterol/50 micrograms glycopyrronium) plus placebo (n = 90) or to receive concurrent indacaterol (150 micrograms) plus glycopyrronium (50 micrograms) (n = 103) for four weeks. The dose of fine-particle indacaterol in the indacaterol/glycopyrronium combination product was reduced from 150 micrograms to 110 micrograms to ensure dose equivalence with the comparator[4].

The primary endpoint was to evaluate the noninferiority of the indacaterol/glycopyrronium combination product compared to concurrent indacaterol plus glycopyrronium in terms of its effect on trough forced expiration volume in one second (trough FEV_1; see Glossary) This was the mean value, at 28 days of measurements at 23 hours, 15 minutes and at 23 hours, 45 minutes after dosing. The primary endpoint was achieved; trough FEV_1 (calculated as the least squares mean ± standard error) for indacaterol/glycopyrronium combination product (1.5 ± 0.02 litres) was noninferior to trough FEV_1 for concurrent indacaterol plus glycopyrronium (1.5 ± 0.18 litres). Secondary endpoints including FEV_1 area under the curve over the four hour period following administration at day 1 and day 28 were similar for the two treatment arms[4]. The proportion of patients with serious adverse events (SAEs) was 4.4% for indacaterol/glycopyrronium combination product treated patients and 5.8% for patients treated with concurrent indacaterol plus glycopyrronium; no discontinuations occurred due to SAEs[1,4].

2.2 Points to note

- For COPD patients eligible to receive a long-acting $beta_2$-agonist (LABA) and a long-acting muscarinic receptor antagonist (LAMA), the fixed dose combination of indacaterol/glycopyrronium offers the convenience of a once daily inhaled dose from a single inhaler in place of separate doses of a LABA and a LAMA from different inhalers[1].
- The trial data showed that the indacaterol/glycopyrronium inhalation powder provided similar clinical efficacy and a similar safety profile to concurrent administration of the two individual components indacaterol maleate and glycopyrronium bromide inhalation powders[4].

3.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

3.1 Budget impact evidence

The company has provided estimates of the budget impact of the indacaterol/glycopyrronium combination product based on the annual cost of the treatment for one patient and estimates of the number of treated patients[1]. Market research data was used to calculate the number of patients in Wales who will receive a LAMA and LABA combination in 2013 as 1,330[1]. The numbers of eligible patients in the years 2014–2019 were obtained by scaling the figure of 1,330 in 2013 using Welsh Government population projections[5], Welsh Quality and Outcomes Framework data for COPD prevalence[6], a COPD incidence figure of 84 per 100,000[7] and Welsh mortality figures for COPD[8,1]. The company estimated market share of the indacaterol/glycopyrronium combination product to be 3% (40 patients) in 2014 rising to 15% (214 patients) in 2018. The annual cost per patient of [Commercial in confidence data removed] leads to projected net costs of [Commercial in confidence data removed] in 2014 increasing to [Commercial in confidence data removed] in 2018 as displayed in Table 1[1].

Table 1. Company estimates of the budget impact of indacaterol/glycopyrronium[1]

Year	2014	2015	2016	2017	2018
Number of patients eligible for LABA plus LAMA	1,349	1,368	1,388	1,408	1,428
Market share	3%	6%	9%	12%	15%
Treated patients	40	82	125	169	214
Net cost	[Commercial in confidence data removed]				

3.2 AWTTC critique of the budget analysis

- The annual cost of the combined indacaterol/glycopyrronium product is [Commercial in confidence data removed] less than the annual cost of the two individual treatments (see Table 2).
- The company have used market analysis data and Welsh Government statistics to estimate number of patients eligible for LABA plus LAMA treatment. The company's projections of net cost are strongly dependant on their estimate of patient uptake and therefore subject to uncertainty.

3.3 Comparative unit costs

Table 2 provides comparative annual acquisition costs for the indacaterol/glycopyrronium combination product and some other LABA plus LAMA treatments.

Table 2. Comparison of costs for LABA plus LAMA combinations

LABA plus LAMA	Recommended dose	Annual cost
Indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) 85 micrograms/43 micrograms inhalation powder*, hard capsule	One capsule daily	[Commercial in confidence data removed] (including the cost of Breezhaler® device)
Indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder†, hard capsule plus **glycopyrronium (Seebri® Breezhaler®▼)** 44 micrograms inhalation powder*, hard capsule	One capsule of each daily	£691 (including the cost of Breezhaler® device)
Indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder†, hard capsule plus **tiotropium (Spiriva® Handihaler®)** 18 micrograms inhalation powder†, hard capsule	One capsule of each daily	£765 (including the cost of Breezhaler® and Handihaler® device)
Salmeterol (Neovent®) 25 micrograms inhalation powder§ plus **tiotropium (Spiriva® Handihaler®)** 18 micrograms inhalation powder†, hard capsule	Two inhalations of salmeterol twice daily and one capsule of tiotropium daily	£747 (including the cost of metered dose inhaler and Handihaler® device)
Indacaterol (Onbrez® Breezhaler®) 150 micrograms inhalation powder†, hard capsule plus **aclidinium (Eklira® Genuair®▼)** 322 micrograms inhalation powder*	One capsule of indacaterol and one inhalation aclidinium twice daily	£704 (including the cost of Breezhaler® device and metered dose inhaler)
Salmeterol (Neovent®) 25 micrograms inhalation powder§ plus **aclidinium (Eklira® Genuair®▼)** 322 micrograms inhalation powder*	Two inhalations of salmeterol twice daily and one inhalation of aclidinium twice daily	£686 (including the cost of metered dose inhalers)
Salmeterol (Neovent®) 25 micrograms inhalation powder§ plus **glycopyrronium (Seebri® Breezhaler®▼)** 44 micrograms inhalation powder*, hard capsule	Two inhalations of salmeterol twice daily and one capsule of glycopyrronium daily	£673 (including the cost of Breezhaler® device and metered dose inaler)
Formoterol fumarate dehydrate (Easyhaler® Formoterol®) 12 micrograms inhalation powder§ plus **glycopyrronium (Seebri® Breezhaler®▼)** 44 micrograms inhalation powder*, hard capsule	One inhalation of formoterol twice daily and one capsule of glycopyrronium daily	£476 (including the cost of Easyhaler® and Breezhaler® devices)
Formoterol fumarate dehydrate (Easyhaler® Formoterol®) 12 micrograms inhalation powder§ plus **tiotropium (Spiriva® Handihaler®**)18 micrograms inhalation powder†	One inhalation of formoterol twice daily and one capsule of tiotropium daily	£551 (including the cost of Easyhaler® and Handihaler® devices)
Formoterol fumarate dehydrate (Easyhaler® Formoterol®) 12 micrograms inhalation powder§ plus **aclidinium (Eklira® Genuair®▼)** 322 micrograms inhalation powder*	One inhalation of formoterol twice daily and one inhalation of aclidinium twice daily	£490 (including the cost of Easyhaler® and metered dose inhaler)

Costs of comparators are based on Monthly Index of Medical Specialities (MIMS) list prices as of October 2013[9].
*Delivered dose; †Capsule dose; §Metered dose
This table does not imply therapeutic equivalence of the stated treatments and doses.
See Summaries of Product Characteristics (SPCs) for full dosing details[2,10–15].

4.0 ADDITIONAL INFORMATION

4.1 Prescribing and supply

AWTTC is of the opinion that, if recommended, indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

The company do not anticipate that indacaterol/glycopyrronium (Ultibro® Breezhaler®▼) will be supplied by a home healthcare provider.

4.2 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

4.3 Evidence search

Date of evidence search: 22 October 2013
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

Chronic obstructive pulmonary disease (COPD)

National Institute for Health and Clinical Excellence (NICE) use the following working definition of COPD:

- Airflow obstruction is defined as a reduced FEV_1/FVC ratio, such that FEV_1/FVC is less than 0.7.
- If FEV_1 is ≥ 80% predicted, a diagnosis of COPD should only be made in the presence of respiratory symptoms, for example breathlessness or cough[16].

FEV_1

The forced expired volume in 1 second is the volume of air that can be expelled from maximum inspiration in the first second[17].

FEV_1% predicted

The forced expiratory volume in one second (FEV_1) expressed as a percentage of a predicted value, calculated using a reference population[17].

FVC

Forced vital capacity is the volume of air that can be forcibly expelled from the lung from the maximum inspiration to the maximum expiration[17].

REFERENCES

1 Novartis Pharmaceuticals UK Ltd. Form C: Limited appraisal submission. Indacaterol maleate/glycopyrronium bromide (Ultibro® Breezhaler®▼). Oct 2013.

2 Novartis Pharmaceuticals UK Ltd. Ultibro® Breezhaler®▼. Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002679/WC500151255.pdf. Accessed Oct 2013.

3 European Medicines Agency. Ultibro® Breezhaler®▼: EPAR - summary for the public. Procedure No.: EMEA/H/C/002679. Oct 2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/document_detail.jsp?webContentId=WC500151258&mid=WC0b01ac058009a3dc. Accessed Oct 2013.

4 Dahl R, Jadayel D, Alagappan VK et al. Efficacy and safety of QVA149 compared to the concurrent administration of its monocomponents indacaterol and glycopyrronium: the BEACON study. *Int J Chron Obstruct Pulmon Dis* 2013; 8: 501-8.

5 Welsh Government. 2010-based principal population projections for Wales, 2010 to 2035. Oct 2011. Available at: https://statswales.wales.gov.uk/Catalogue/Population-and-Migration/Population/Projections/National/2010-Based/PopulationProjections-by-Year-Gender. Accessed Oct 2013.

6 Welsh Government. Patients on quality and outcomes framework (QOF) by local health board and disease registers. Oct 2013. Available at: https://statswales.wales.gov.uk/Catalogue/Health-and-Social-Care/NHS-Primary-and-Community-Activity/GMS-Contract/PatientsOnQualityAndOutcomesFramework-by-LocalHealthBoard-DiseaseRegister. Accessed Oct 2013.

7 European Respiratory Society. European Lung White Book, part 2 Major respiratory diseases, 03 COPD. Nov 2003. Available at: http://dev.ersnet.org/uploads/Document/45/WEB_CHEMIN_1263_1168339451.pdf. Accessed Oct 2013.

8 Welsh Government. Deaths by cause. Apr 2013. Available at: https://statswales.wales.gov.uk/Catalogue/Health-and-Social-Care/Births-Deaths-and-Conceptions/Deaths/Deaths-by-Cause. Accessed Oct 2013.

9 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). Oct 2013. Available at: http://www.mims.co.uk/. Accessed Oct 2013.

10 Novartis Pharmaceuticals UK Ltd. Onbrez® Breezhaler®. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/emc/medicine/23260/SPC/Onbrez+Breezhaler+150+and+300+microgram+inhalation+powder%2c+hard+capsules/. Accessed Oct 2013.

11 Novartis Pharmaceuticals UK Ltd. Seebri® Breezhaler®▼. Summary of Product Characteristics. Nov 2012. Available at: http://www.medicines.org.uk/EMC/medicine/27138/SPC/Seebri+Breezhaler+Inhalation+Powder%2c+Hard+Capsules+44mcg/. Accessed Oct 2013.

12 Boehringer Ingelheim Ltd. Spiriva®. Summary of Product Characteristics. Oct 2013. Available at: http://www.medicines.org.uk/EMC/medicine/10039/SPC/Spiriva+18+microgram+inhalation+powder%2c+hard+capsule/. Accessed Oct 2013.

13 Almirall Ltd. Eklira® Genuair®▼. Summary of Product Characteristics. Jul 2013. Available at: http://www.medicines.org.uk/EMC/medicine/27001/SPC/Eklira+Genuair+322+micrograms+inhalation+powder/. Accessed Oct 2013.

14 Orion Pharma (UK) Ltd. Formoterol Easyhaler®. Summary of Product Characteristics. Mar 2013. Available at: http://www.medicines.org.uk/emc/medicine/19503/SPC/Formoterol+Easyhaler+12+micrograms+per+actuation+inhalation+powder/. Accessed Nov 2013.
15 Fannin UK Ltd. Neovent®. Summary of Product Characteristics. Jun 2012. Available at: http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm?prodName=NEOVENTTM%20CFC-FREE%20INHALER%2025%20MICROGRAMS%20PER%20ACTUATION%20PRESSURISED%20INHALATION%20%20SUSPENSION.&subsName=&pageID=ThirdLevel&searchTerm=neovent#retainDisplay. Accessed Nov 2013.
16 National Institute for Health and Clinical Excellence. Clinical Guideline 101. Chronic obstructive pulmonary disease. Jun 2010. Available at: http://guidance.nice.org.uk/CG101. Accessed Oct 2013.
17 Egton Medical Information Systems Limited. Measurements made in spirometry. 2012. Available at: http://www.patient.co.uk/doctor/Spirometry-Calculator.htm . Accessed Oct 2013.